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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,072	10/14/2005	Ralf-Holger Voss	BB.140	1890

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
03/11/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/529,072	VOSS ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12,16-19 and 32-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12,16-19 and 32-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 12-24-09 has been entered. Claims 1, 3, 6, 17 and 32 have been amended. Claims 13-15 and 29-31 have been canceled. Claims 34-42 have been added. Claims 1-9, 12, 16-19 and 32-42 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 36, 39 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant's amendment filed 12-24-09 necessitates this new ground of rejection.

The phrase "wherein said TCR is human" in claims 36, 39 and 42 is vague and renders the claims indefinite. TCR is a T cell receptor. It is unclear how a T cell receptor can be "human". A protein is not "equal" to a human.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9, 12, 16-19, 32 and 33 remain rejected and newly added claims 34-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a method for producing a TCR complex wherein the alpha- and beta-chains of an MDM2(81-88)-specific TCR are used as alpha-chain and beta-chain, and wherein the Gly192 of the constant region of the alpha-chain and the Arg208 of the constant region of the beta-chain are exchanged by Arg 192 in the constant region of the alpha-chain and by Gly208 in the constant region of the beta-chain, does not reasonably provide enablement for a method in vitro, for producing any other hetrodimeric specific wild-type or chimeric TCR having any antigen specificity, wherein glycine, serine, threonine, valine, or alanine is introduced after the mutagenesis of the DNA molecule that introduces the sterically recessed group including Arg208, and glutamine, glutamic acid, alpha-methylvaline, histidine, hydroxylysine, tryptophan, lysine, arginine, phenylalanine or tyrosine is introduced after the mutagenesis of the DNA molecule that introduces the sterically projecting group including Gly192. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 9-25-09. Applicant's arguments filed 12-24-09 have been fully considered but they are not persuasive.

Applicant argues that the claims indicate that the mutations are to be made at amino acid-surface in the TCR constant domain and the actual biological function of the TCR would not be disturbed. Substitution of similar amino acids often does not lead to changes in biological function and the structure/function of the altered polypeptide in the instant application is well-known in the art and TCR have been extensively studied. The constant domains of TCRs are highly conserved, over 95% homology, and standardized and dedicated numbering and homology system existed for TCR (ImMunoGeneTics Information System). Applicant further

cites reference Voss et al., 2008, and argues that the TCR modification was equally efficient on both Mu and Hu TCR and this approach is generally applicable to TCR independently of their Ag specificity and affinity, subset distribution, and species of origin (e.g. p. 9-11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 9-25-09. The claims read on substituting or mutating various amino acid positions in numerous different TCRs derived from numerous organisms with recited amino acid residues. It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. The biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention and even same short stretch of amino acid sequence can show diverse biological functions while surrounded by different background amino acid sequences. Different amino acid substitutions or mutations in various TCRs can result in diverse TCR antigen specificities and its signaling functions, and the effect of the amino acid substitutions or mutations on the TCR antigen specificities and its signaling functions would be unpredictable at the time of the invention. The amino acid residues introduced after the mutagenesis of the DNA molecules include hydrophobic, hydrophilic, neutral, positively and negatively charged amino acid residues. Whether such substitution will affect the biological function or specificity of TCRs depend on the type of amino acid residue being substituted and its position in TCR constant domain, and the type of amino acid residue used for substitution. The resulting biological

functions of the substituted or chimeric TCRs would be unpredictable at the time of the invention.

Further, different TCRs derived from various organisms could have different amino acid sequences and it is not necessary that Glycine would be at amino acid position 192 of various alpha-chain and Arginine would be at amino acid position 208 of various beta-chain of TCRs. When Glycine is not at amino acid position 192 of alpha-chain and when Arginine is not at amino acid position 208 of beta-chain, one skilled in the art at the time of the invention would not be able to perform the claimed method to produce a T-cell expressing a T-cell receptor (TCR). Although the constant domain of TCRs may be highly conserved among a few species, however, there is no evidence of record that shows Glycine would be at amino acid position 192 of various alpha-chain and Arginine would be at amino acid position 208 of various beta-chain of TCRs from various organisms. It is noted that even TCRs for different antigen specificities could have diverse amino acid sequences. The cited Voss reference points out that the approach of TCR modification may be applicable to TCR independently of their Ag specificity and affinity, subset distribution, and species of origin. However, it does NOT mean that the claimed substituted or chimeric TCRs would not impair the biological function of the wild-type TCR. As discussed above, whether such substitution will affect the biological function or specificity of TCRs depend on the type of amino acid residue being substituted and its position in TCR constant domain, and the type of amino acid residue used for substitution. The resulting biological functions of the substituted or chimeric TCRs would be unpredictable at the time of the invention. Thus, the claims remain rejected under 35 U.S.C. 112, first paragraph.

Conclusion

No claim is allowed.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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